5-2016

Comparison of Red Yeast Rice Versus Statin Therapy for Dyslipidemia: A Literature Review

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Project Proposal

Comparison of Red Yeast Rice Versus Statin Therapy for Dyslipidemia: A Literature Review

Statins are the first line treatment for hyperlipidemia. However, some patients do not tolerate statins. For these patients, alternative treatments such as red yeast rice may be considered. The purpose of this literature review is to compare the lipid lowering capability of red yeast rice to statins.

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ACCEPTANCE

This research project, *Comparison of Red Yeast Rice Versus Statin Therapy for Dyslipidemia: A Literature Review* by Ellison Croft, Michelle Ladewig, and Autumn Mills, was prepared under the direction of the candidate's Advisor. It has been approved and accepted in partial fulfillment of the requirements for the degree of Master of Science in the Department of Nursing in the College of Health Science and Professions, University of North Georgia.

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COMPARISON OF RED YEAST RICE VERSUS STATIN THERAPY FOR DYSLIPIDEMIA: A LITERATURE REVIEW

by

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A RESEARCH PROJECT

Presented in Partial Fulfillment of Requirements for the
Degree of Master of Science
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Dahlonega, Ga

2016

ABSTRACT

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Statins are the first line treatment for hyperlipidemia. However, some patients do not tolerate statins. For these patients, alternative treatments such as red yeast rice may be considered. The purpose of this literature review is to compare the lipid lowering capability of red yeast rice to statins.

Introduction

Cardiovascular disease is the leading cause of mortality worldwide, with hyperlipidemia being an important risk factor (Li et al., 2014). Treatment with 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors, better known as statins, are the recommended first line therapy for hyperlipidemia (Stone et al., 2013). These medications are generally well tolerated but may have multiple side effects resulting in up to 40 percent of patients discontinuing their use within one year (Becker, French, Morris, Silvent, & Gordon, 2013). This is one reason many providers seek alternative lipid lowering agents.

One of the more common alternative medications used for lowering lipids is red yeast rice, a traditional Chinese medicine prepared using *Monascus purpureus* fermented on rice (Liu et al., 2006). This literature review was conducted to evaluate the effectiveness of red yeast rice in comparison to statins for the treatment of hyperlipidemia. Specifically, the literature review will seek to compare these two medications in their effectiveness in lowering LDL levels. Lowering LDL level is a focus of the treatment guidelines for hyperlipidemia and an important factor in lowering the risk of cardiovascular disease and events. The clinical question in need of answer is "In adults with hyperlipidemia, does red yeast rice compare to recommended statin therapy in lowering LDL percentages?" The answer to this question could pose alternative treatment options for patients with hyperlipidemia.

Problem Statement

Hyperlipidemia is an important disease that, if not corrected, can lead to further complications including coronary artery disease, peripheral vascular disease, and cerebrovascular disease. One of the goals of treatment is to lower LDL levels, which can be done with lifestyle modification in addition to medication. The first line drug of choice is a statin which is shown to

decrease LDL levels by 30 to 50 percent with a moderate intensity statin and greater than or equal to 50 percent with a high intensity statin (Stone et al., 2013). However, these medications carry the risk of side effects that are often intolerable with patients reporting 68% myalgias, 8% elevated liver enzymes, and 16% gastrointestinal disturbances (Venero, Venero, Wortham, & Thompson, 2010). In more rare instances myositis and rhabdomyolysis are serious complications of statin therapy (Becker, Gordon, French, Morris, & Rader, 2009). For these reasons, there are a growing number of patients that practitioners must consider alternative therapies to treat hyperlipidemia.

One of the most common alternative medications used in the treatment of hyperlipidemia is red yeast rice. The goal of this literature review was to evaluate the effectiveness of red yeast rice in lowering LDL levels in comparison to statins. By reviewing the evidence, the nurse practitioner can evaluate the possibility of red yeast rice to be recommended as an alternative treatment for hyperlipidemia if statins are not tolerated or desired by the patient.

Process of Discovery

A search of literature was conducted using the following databases from 1999 to August 2015: the Cochrane library, the Cumulative Index of Nursing and Allied Health Literature (CINHAHL), MEDLINE, EBSCO host, ProQuest, National Institutes of Health (NIH), and Up to Date. Search terms included red yeast rice (RYR), statin, lipids, dyslipidemia, low density lipoprotein (LDL), hypercholesterolemia, and hyperlipidemia. MeSH terms used were Chinese red yeast rice dietary supplement and hydroxymethylglutaryl-CoA reductase inhibitors. Only articles written in English were selected. Animal studies were included and articles were not limited based on country of origin. The reference lists of each identified article was also screened for additional studies and review articles. A total of 14 articles were reviewed, 3 were eliminated

due to lack of specificity to red yeast rice. Zotero was used to store and organize articles as well as aid in developing reference list. The 2013 American College of Cardiology and American Heart Association (ACC/AHA) guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults was utilized to determine treatment of hyperlipidemia with statin therapy. To evaluate the quality of research, the articles were scored from level one to six which include systematic reviews, randomized control trials, cohort studies, case-control studies, case reports, and expert opinions (Melnyk & Fineout-Overholt, 2015). An evidence table was created to identify key components of research and its findings.

Critical Appraisal of Related Evidence

Abdelbaset, Safar, Mahmoud, Negm, & Agha (2014) conducted a randomized control trial (RCT) on 70 Wistar rats that were rendered hyperlipidemic through a high fat diet for 90 days. This trial was conducted to examine the efficacy and safety of RYR compared to atorvastatin. Atorvastatin decreased LDL which was statistically significant compared to hyperlipidemic control group and the normal control group at days 15 and 30. Cholesterol was lowered by RYR plus coenzyme Q10 (CoQ10) without elevating creatine kinase (CK) whereas atorvastatin had a rise in CK twofold the normal value after 30 days. Atorvastatin increased levels of aspartate aminotransferase (AST) levels whereas RYR did not. Normal levels of CoQ10 in the heart were maintained with RYR which are essential components for energy production in muscles. This is thought to offset elevated CK which is considered to be the hallmark of myopathy. Limitations of this study include that the study was conducted in rats rather than humans, and a p value was reported to show what was statistically significant but the data was not reported with p values making data interpretation difficult. The strength of this study was the tightly controlled populations and that it provided data on several factors that play a role in

myalgia. This article provided a level two evidence based on the hierarchy of evidence table. (Melnyk & Fineout-Overholt, 2015).

Becker, French, Morris, Silvent, and Gordon (2013) conducted a randomized, double blind placebo controlled trial in Pennsylvania. The results were used to determine the effects of phytosterol tablets as well as lifestyle changes in addition to RYR in patients who have refused statin therapy or had statin associated myalgias. The trial was completed on a total of 187 patients ages 21 to 80 with a mean age of 62 in which 75% were women. The mean LDL was 154 with LDL ranges being kept between greater than 100 and less than 210. This trial had an attrition rate of 32. The subjects were randomized into four groups. There were 55 people in the RYR plus phytosterols plus lifestyle change group. There were 54 in the RYR plus placebo plus lifestyle change group. In the third group there were 56 who took RYR in addition to phytosterols plus participating in usual care. The fourth group had 55 participants which took RYR plus placebo and usual care. RYR was statistically significant in decreasing LDL, total cholesterol (TC), triglyceride (TG), and increasing HDL ($p< 0.001$). However, it did not statistically reduce C-reactive protein ($p=0.045$). Lifestyle changes group participants were 2.3 times more likely to achieve an LDL less than 100mg/dL in addition to significantly more weight loss. The phytosterols had no significant changes in any of the categories ($p< 0.37$). The limitations of this study are that the attrition rate was high and participants had to take 10 pills which could limit compliance. Whereas the strengths of this study were that it highlighted RYR efficacy compared to not only atorvastatin but to lifestyle changes and phytosterols. The evidence of this article is of a level two in the hierarchy of evidence (Melnyk & Fineout-Overholt, 2015).

Becker, Gordon, Halber, French, Morris, and Rader (2009) conducted a RCT which was carried out in a community based cardiology practice in Philadelphia, PA. The trial studied the effectiveness as well as the tolerability of RYR and therapeutic lifestyle changes for treatment of dyslipidemia in patients that could not tolerate traditional statin therapy. The study had 62 participants diagnosed with dyslipidemia in addition to a history of stopping statin therapy due to myalgias. All patients were concomitantly enrolled in a therapeutic lifestyle change program. The trial randomly assigned participants into a groups that received RYR or a placebo. The mean age in RYR group was 60.5 and the mean age in placebo group was 61.5. The study had an attrition rate of four patients. Sixty five percent of patients were female. The RYR group's LDL level was significantly lower than in the placebo group at both weeks 12 ($P<0.001$) and 24 ($P= 0.011$). Levels of HDL, triglycerides, liver enzymes, CPK levels, weight loss, and pain severity scores did not differ between groups. The limitation in this trial was that it was small, a single site, a short duration, and it focused on laboratory measures only. Also, because RYR is regulated as a dietary supplement instead of a medication, the consistency of dosing cannot be verified. It was also noted by researchers that even though RYR decreased LDL it did not achieve LDL levels below 100 mg/dL in 70% of participants which they attributed to the weak potency of the RYR product. The strength of this study was that it highlighted further areas needed for research on RYR to provide additional option in lowering LDL. Level two evidence is provided in this trial based on hierarchy of evidence table (Melnyk & Fineout-Overholt, 2015).

Gerards, Terlou, Yu, Koks, and Gerdes (2015) performed a meta-analysis conducted via the preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines. The outcome was to verify the safety and effectiveness of RYR for the reduction of LDL cholesterol. Twenty RCTs were analyzed from EMBASE and Medline with a total of 6663

participants that were located in Taiwan, Norway, China and the United States. In the studies that compared RYR to a placebo, LDL decreased −1.02 mmol/L in RYR compared to placebo resulting in a corresponding cardiovascular risk reduction of 15–20%. In RYR compared to a statin drug, there was no statistically significant difference between groups. In the studies comparing RYR to a non-statin control group, LDL was reduced in RYR groups 0.52 mmol/L higher than the control group. All of these findings were statistically significant. This meta-analysis also examined the incidence of adverse effects to evaluate the safety of RYR. In summary, there was no statistical significance in adverse effects of liver and kidney functions as well as myalgias and nonspecific complaints in RYR and control groups. A strength of this meta-analysis was the detailed analysis of adverse reactions that could be attributed to RYR. A limitation was that a p value was reported but the data did not include the p values making it difficult to interpret statistical significance. Another limitation was the differences in design and primary outcomes of the studies analyzed, and the majority of studies did not contain enough data on safety. Risk of bias was high on evaluating patient reported symptoms and was recognized by the researchers. This article provided a level one quality of research in regards to the hierarchy of evidence table (Melnyk & Fineout-Overholt, 2015).

Halbert et al. (2010) performed a double blind RCT to compare the tolerability of RYR to pravastatin. Forty three participants in Philadelphia, PA with documented statin associated myalgia leading to discontinuation of at least one statin other than pravastatin were selected. The participants had a mean age of 62.7, 74.4% were women, and attrition rate of 2. Participants were randomly assigned either 2,400 mg RYR twice a day or pravastatin 20 mg twice a day for 12 weeks. The primary outcome measured was the daily pain scores and the incidence of treatment discontinuation due to myalgia. The secondary outcomes evaluated were plasma lipid

levels. No statistically significant differences were found in the mean muscle strength scores between the two groups at week 4, 8, and 12 or the incidence of treatment discontinuation because of myalgia (5% in RYR group and 9% in pravastatin group). Also, no statistically significant differences were found between the two groups in the mean LDL ($p = 0.194$), TC ($p = 0.23$), TG ($p = 0.96$), or HDL ($p = 0.114$). A strength of this article is that it was the first randomized double blind trial to compare the tolerability of RYR to a stain in a population with statin induced myalgias. Limitations included a small sample size and short duration of the study. This research was a level two in the hierarchy of evidence table (Melnyk & Fineout-Overholt, 2015).

Heber et al. (1999) completed a 12 week randomized, double blind, placebo controlled trial in California. The trial included 88 patients consuming a diet similar to the American Heart Association Step One diet to evaluate the cholesterol lowering effects of RYR supplements separate from diet alone. Fasting blood samples of TC, TG, LDL, and HDL were taken at initiation of the trial and at week 8, 9, 11, and 12. At initiation and at week 12 a metabolic panel was also done for assessment of liver and renal function tests. Subjects in the test group were given capsules of 2.4g of RYR daily versus the placebo group which was given capsules of rice powder placebo daily. The RYR group showed a decrease in TC ($P<0.05$), TG ($P=0.05$), and LDL ($P<0.001$) greater than the placebo groups at weeks 8 and 12 of evaluation. Levels of HDL were not statistically significant. Limitations to the research include dietary changes that were not controlled by the researcher, and recruitment of subjects was done by newspaper advertisements and posted announcements. A strength of the study was that measurements were collected and analyzed at multiple points within the study. Utilizing the hierarchy of evidence table this research was rated a level two (Melnyk & Fineout-Overholt, 2015).

Liu et al. (2006) performed a meta-analysis of 93 RCTs found in 5 databases (PubMed, CBMdisk, TCMLARS, the Cochrane Library, and AMED) that compared RYR to either a placebo, no treatment, a statin, or other lipid lowering agents. From the 93 RCTs there was a total 9625 participants in which settings were not specified. Three RYR preparations were utilized including cholestin, Xuezhikang, and Zhibituo. Of the 93 articles, 91 trials were published in Chinese and 2 in English with a time frame ranging from 4 to 24 weeks. Serum levels were compared for TC, TG, LDL, and HDL. Adverse effects that were studied varied and were not measured by a stated scale. Cost effectiveness was studied and reported in United States dollars. Cholestin lowered TC ($p<0.00001$), TG ($p=0.38$), LDL ($p<0.00001$). Xuezhikang lowered TC ($p<0.00001$), TG ($p=0.001$), and LDL ($p<0.00001$) and increased HDL ($p=0.73$). Zhibituo decreased TC ($p<0.00001$), TG ($p<0.00001$), did not decrease LDL ($p=0.34$), and did increase HDL ($p<0.0001$). A P value of < 0.10 was statistically significant. Limitations of this meta-analysis were listed by the reviewers and included insufficient reporting of generation methods of the allocation sequence, allocation concealment, and double blinding. Reviewers also recognized limited description of study design, possible publication bias in some countries, and variations in RYR preparations. A strength was the number of studies reviewed. Utilizing the hierarchy of evidence table this research was rated a level one (Melnyk & Fineout-Overholt, 2015).

Li et al. (2014) performed a meta-analysis of RCTs conducted according to the PRISMA statement. Six databases were searched up to August 2013 (PubMed, the Cochrane Library, EBSCO host, Chinese VIP Information, China National Knowledge Infrastructure, and Wanfang). A total of 13 RCTs were chosen with 804 participants from the combined trials in which settings were not specified. All trials were published in English with treatment of 4 weeks

or longer. Serum levels for TC, TG, LDL, HDL, ALT, AST, creatinine, CK, and fasting blood glucose measured via serum hemoglobin HbA1c were compared. In all 13 studies TC was lowered by RYR ($P<0.001$). In 11 studies TG were lowered by RYR ($p<0.001$) but were not reported in 2 studies. In all 13 studies LDL was lowered ($p<0.001$). Effect of RYR on HDL had varying results ($P=0.11$). A p value of < 0.05 was statistically significant. Limitations of this meta-analysis were that HDL results were only significant in European studies; heterogeneity of some outcomes which may be related to some populations, doses, and durations of treatment; dietary, lifestyle, and certain medicines were not regulated within study; small sample size; outcomes were surrogate indices. Utilizing the hierarchy of evidence table this research was rated a level one (Melnyk & Fineout-Overholt, 2015).

Venero, Venero, Wortham, and Thompson (2010) conducted a retrospective observational study of a clinical population at the Hartford Hospital Cholesterol Management Center in Connecticut. Their efforts were to evaluate the efficacy of RYR in lowering LDL in patients that were intolerant to statin therapy. Twenty five participants were found that were intolerant to daily statin use and had been treated with RYR for greater than or equal to 4 weeks. While the primary objective was to monitor LDL levels, secondary outcomes of TC, HDL, TG, CPK, and ALT were evaluated. It was found that LDL lowering was statistically significant ($p< 0.001$) as well as TC decrease ($p< 0.001$). The HDL increase ($p=0.48$) and TG levels ($p=0.06$) were not statistically significant. Limitations of this study were that it was unblinded, small, uncontrolled, retrospective, and did not report levels of CPK or ALT even though it stated these levels were drawn. Other limitations include that adherence to treatment was not monitored, labs were drawn at various clinical laboratories, markers of inflammation or endothelial dysfunction were not monitored, and evaluation for renal function was not monitored despite known

nephrotoxins in some RYR preparations. The reviewers identified the strength of this study was that it provided real world efficacy of RYR in reducing LDL using over the counter RYR. Using the hierarchy of evidence table this retrospective study provides level three evidence (Melnyk & Fineout-Overholt, 2015).

Verhoeven et al. (2013) performed a double blinded, placebo controlled, RCT in Belgium with 52 physicians and spouses with a TC greater than 200. The mean age was 55, with 31 participants in the intervention group and 21 in the placebo group. Fifty two percent were male, 48% were female, and attrition was not listed. The participants were randomly selected to receive a RYR extract or placebo for eight weeks. The primary outcome measured was to compare the before and after differences in lipid levels. A secondary outcome measured was reported side-effects, CK elevation, and a change in cardiovascular risk. Statistically significant findings included a TC decrease 14.62% ($p<.001$) and LDL 22.17% ($p<.001$) in the RYR group but the changes in HDL and TG was not found to be significant. Systematic Coronary Risk Evaluation (SCORE) was decreased in 5 out of 31 patients of the intervention group. Strengths of this research were that both sexes were represented almost equally and a specific amount of Monacolin K in the RYR supplement was measured and given. Limitations included a small sample size, statistical significance was not listed for CPK or side effects and the study short duration. This article was given a level two based on the hierarchy of evidence (Melnyk & Fineout-Overholt, 2015).

Yang and Mousa (2012) performed a literature review of 22 RCTs consisting of a total of 11,019 participants in United States, Italy, China, Taiwan, and Norway. The primary objective was to review the effectiveness of RYR on hyperlipidemia. The secondary objective was to review other uses of RYR. Statistically significant findings in the RYR versus placebo trials

included reduction in TC by 15.5%, 23.7%, and 14.9% ($p<0.001$). A significant reduction in LDL cholesterol by 23%, 27.7%, and 21.3% ($p<0.001$) was also observed in these studies. In the Taiwan study, a reduction in TG was found ($p<0.05$). In the RYR compared to statin RCTs, there were no differences between the RYR and Pravastatin group with regard to TC (23% decrease, $p=0.23$), LDL (30.2% decrease, $p=0.194$), TG (7.8% decrease, $p=0.96$), or HDL (3.8% increase, $p=0.114$). In relation to coronary heart disease, the article stated that RYR significantly decreased the risk of non-fatal MI events and overall coronary heart disease (CHD) events when compared to a placebo, but failed to demonstrate an effect in other CHD endpoints. However, specific p values or data to support this statement was not identified in the article. Diabetes study findings were inconclusive. Strengths of this literature review include that the researchers listed the weaknesses of the trials and identified the need for more rigorous testing prior to making recommendations for practice. Limitations included differences in study organization and methods; some studies had small populations, short durations, single-sited or single ethnicities represented. Also, the authors only gave the results and did not mention any of the measurement tools or data analysis. Another limitation was that the authors created a table with level of evidence of RYR use based solely on their literature review. This table could be misinterpreted as a guideline recommendation as the authors used the A, B, C, D format for classification of scientific evidence. Overall, this article is a level four in the hierarchy of evidence pyramid (Melnyk & Fineout-Overholt, 2015).

Synthesis of Related Evidence

Hyperlipidemia guidelines and statin effects on LDL

The 2013 American College of Cardiology and American Heart Association guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults

states that high intensity statins should be used in patients between 21 and 75 years of age with LDL greater than or equal to 190 mg/dL (Stone et al., 2013). Patients with clinical atherosclerotic cardiovascular disease (ASCVD) should also receive high intensity statins. If LDL is between 70 and 189, patient has diabetes, or between ages 40-75 with an estimated 10 year ASCVD risk greater than or equal to 7.5% a high intensity statin is recommended. High intensity statins include atorvastatin 40-80 mg and rosuvastatin 20-40 mg. These statins are reported to lower LDL approximately greater than or equal 50%.

Moderate intensity statins are recommended when patients are not a candidate for high intensity statin and if ASCVD risk score is less than 7.5% (Stone et al., 2013). Examples of moderate intensity statins include daily atorvastatin 10-20 mg, rosuvastatin 5-10 mg, simvastatin 20-40 mg, pravastatin 40-80 mg, lovastatin 40 mg, and fluvastatin 40 mg BID. Moderate intensity statins are reported to lower LDL by approximately 30% to less than 50%.

The 2013 ACC/AHA guideline states that a low intensity statin is not recommended for any groups except if unable to tolerate higher doses. Patients may not be candidates for high intensity statin therapy if they have had previous statin intolerance including gastrointestinal disturbances, increased CK or liver function tests (LFTs), myalgias, or rhabdomyolysis with statin therapy. Contraindications to statin therapy include elevated LFTs, known liver disease, impaired renal function, allergy, or pregnancy.

RYR effects on LDL

All 11 articles evaluated for this literature review showed a statistically significant reduction in LDL with RYR treatment alone. However, four of the 11 articles examined RYR in combination with either lifestyle changes or other supplements such as CoQ10 and phytosterols. The remaining seven articles examined RYR treatment alone and its effect on LDL. Comparison

of the RYR effects on LDL is difficult due to the variability of the dosages and preparations that were given, the time frames of the studies, and the way in which the data was given in the articles reviewed. Six of the articles merely presented the data as p values or mmol/L rather than a comparison of percentages that LDL was decreased. From the five articles that provided the percentages, LDL reduction ranged from 20.2%-32%. Halbert et al. (2010) reported a 30% reduction in LDL when taking RYR compared to a 27% reduction with pravastatin.

Adverse effects of RYR versus statin

All of the articles evaluated side effects from RYR treatment, either self-reported or found on lab testing. The self-reported side effects from nine out of 11 articles included myalgias, muscle weakness, gastrointestinal disturbances, headache, dizziness, alopecia, arthralgia, and allergic reaction. Two articles did not state any self-reported side effects from RYR. In five of the articles, participants in the placebo groups also reported side effects. Therefore, self-reported complaints may be biased. Although these reports were in a small percentage of participants, this data was comparable to the percentages of complaints reported in the placebo or control groups. Differences in reporting this data amongst the articles made it is difficult to summarize the amount of participants that reported adverse side effects.

Four of the articles reviewed had adverse lab outcomes with RYR treatment including elevated LFTs and CK. Within those articles, Li et al. (2014) specifically stated that although LFTs were elevated from baseline with RYR treatment they did remain within normal limits. Yang and Mousa (2012) was the only article to report severe elevation in ALT (1034 U/L with a normal range of 9-72 U/L) with a fever which subsided with discontinuation of the RYR.

Of the five articles that compared statin to RYR treatment, two articles did not list the adverse outcomes of statins. Abdelbaset et al. (2014) reported atorvastatin increased CK twofold

the normal value after 30 days and AST increase was statistically significant ($p<0.05$). Gerards et al. (2015) reported muscle symptoms in RYR vs control group, which included statins and other therapies, that was not statistically significant ($p=0.00$). From this meta-analysis, one study compared reported the risk for developing muscle symptoms in the RYR group was decreased compared to the pravastatin group ($p=0.13$). Halbert et al. (2010) reported myalgias in RYR groups were 5% and in pravastatin groups were 8%. In this article, non-myalgia complaints were comparable between the RYR and pravastatin groups. Treatment discontinuation due to myalgias was not statistically significant between the RYR and pravastatin groups ($p=0.99$).

Solution to the clinical question

There is statistically significant evidence provided by the 11 articles reviewed that supports that RYR is comparable to statin therapy in reducing LDL levels in patients with hyperlipidemia. While the 2013 ACC/AHA hyperlipidemia guidelines do not incorporate RYR therapy as a treatment option, these articles provide evidence of RYR as a valid treatment option. This information could be implemented by adding an addendum to the current guideline.

Proposed Application and Evaluation

Before an addendum could be made to the current guideline, there are several important aspects that require further research. An established dosage would need to be determined for RYR therapy because the articles reviewed gave RYR dosages that ranged from 600 mg to 4800 mg daily. Also, frequency of dosing varied from daily to twice daily and would need to be standardized.

Currently, RYR is not regulated by the FDA and is therefore considered a dietary supplement rather than a medication. Poorly manufactured RYR preparations may contain nephrotoxic substances such as citrinin, which is a toxic metabolite produced by the fungi family

(Becker et al., 2013). Standardization of RYR preparations is recommended to avoid nephrotoxic substances. Based on the strain of *Monascus purpureus* used in the preparation of the RYR supplement, the lipid lowering strength may vary. Standardizing the RYR preparation would also control the concentration of lipid lowering strength in each dose. Regulation of RYR will provide a safer product for recommending to patients.

Additional studies would be needed to implement this plan and would require unknown costs. However this may be offset in the long run by the savings from lower costs of RYR. Liu et al. (2006) reports that for a reduction of 1 mmol/L LDL, the RYR supplement *Xuezhikang* would cost 59 US dollars compared to 84 dollars for pravastatin. Heber et al. (1999) reported that currently available RYR preparations cost 20-30 US dollars per month whereas cholesterol lowering medicines cost 120-300 dollars per month. However, this study is more than 10 years old and is not specific to statin costs. The current insurance coverage for statins lowers the overall cost to patients. If RYR could be regulated as a medication instead of a dietary supplement there is potential for insurance coverage of RYR also.

Implementation of RYR as a standard therapy cannot be recommended until it is FDA regulated, studies are performed on safety of preparations, and the dosage is standardized. At this point, the recommendation is to continue statin use based on current ACC/AHA hyperlipidemia guidelines. Providers can consider the use of RYR in patients that are resistant to taking statins or have had statin associated myalgias, however, they may be hesitant to accept RYR as an alternative to statins until regulation and safety can be determined. Patient acceptance of RYR use would be based on provider recommendations, patient preferences, out of pocket costs, and documented patient outcomes. If RYR became FDA regulated and implemented as a

hyperlipidemia treatment, further studies would then need to be done to evaluate the effectiveness of the new RYR preparation as a lipid lowering agent.

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